IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

PATENT

In re application of: Charych, et al.

Application No.: 09/874,091

Filed: June 4, 2001

Title: MICROARRAYS FOR PERFORMING PROTEOMIC ANALYSES

Attorney Docket No.: CHIRP014

Examiner: Tran, My-Chau T.

Group: 1641

PRE-APPEAL BRIEF REQUEST FOR REVIEW

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Applicants request review of the final rejection in the above-identified application. No amendments are being filed with this request.

This request is being filed with a Notice of Appeal.

The review is requested for the reasons stated on the attached sheets.

Remarks begin on page 2 of this paper.

REMARKS and ARGUMENTS

Claims 1, 60-73 and 79-91 and 97-101 are pending in the application. Independent claims 1 and 73, have been rejected under 35 U.S.C. §103(a) as being unpatentable over US Patent No. 5,478,527 to Gustafson et al. ("Gustafson") in view of US Patent No. 5,478,527 to Chenchik et al. ("Chenchik"). Dependent claims 60-72, 79-91 and 97-101 have also been rejected over the combination of Gustafson and Chenchik, either alone or in further combination with another reference.

Applicants reassert that the differences between the arrays and associated assay techniques of Gustafson are so different from the currently pending claims as well as the other cited references that the Examiner has not asserted a prima facie case of obviousness. Accordingly, Applicants request review.

The Pending Claims

The pending claims are directed to particular arrays of protein-binding agents stably attached to the surface of a solid support, and kits incorporating such arrays. The arrays and kits are used for conducting proteomic analyses such as differential binding assays in which the binding of a particular protein, that has been labeled with a fluorescent dye, to an array element is detected by a fluorescence-based detection system (see, e.g., page 28, line 3 to page 30, line 13 and page 33, line 32 to page 34, line 7). The arrays are designed to optimize the effectiveness of this fluorescence-based detection system.

The claims have previously been focused on a particular embodiment of the invention in hopes of expediting prosecution. These claims recite an embodiment of the invention wherein an aluminum on glass substrate surface is coated with a particular configuration of silicon dioxide on the aluminum substrate surface. Claims 1 and 73 recite that the solid substrate has a substantially planar surface comprising a layer of aluminum formed on a glass base material, the aluminum coated with a silicon dioxide coating having a thickness of between about 200 and 900Å. Importantly, the claims require a plurality of different protein-binding agents bound to the substrate. Claims 73 and 99 further recite that the array includes at least two proteins labeled with different fluorescent labels, bound to one or more of the protein-binding agents.

The Cited References

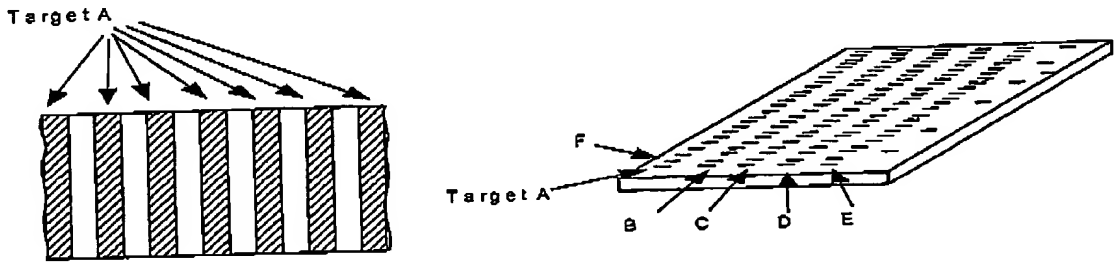
As indicated above, the independent claims are rejected over Gustafson in view of Chenchik. Gustafson and Chenchik describe very different products to be used in very different assays. The primary reference, Gustafson, is specifically addressed to providing a suitable substrate for its reflective diffraction biograting. Chenchik, by contrast, relates to arrays of multiple polymeric targets used to assay labeled probes.

The diffraction biogratings of Gustafson are formed by parallel linear zones of a single active and deactivated binding reagent. The zones form a diffraction grating when the active reagent binds with its opposite member of its binding pair. (col. 1, lines 25-35 and 44-49). In various embodiments, Gustafson describes substrates composed of silicon applied over silicon dioxide (e.g., see Fig. 4) and in which silicon dioxide is applied over a reflective metal deposited on silicon. The objective is to provide an optically flat reflective substrate that apparently enhances reflective diffraction from a biograting formed on the substrate.

As described in Gustafson, diffraction gratings work by causing incident light to be diffracted into specific angles as opposed to being scattered in all directions. The diffraction biogratings of Gustafson are formed by parallel linear zones of a single active and deactivated binding reagent. The zones form a diffraction grating when the active reagent binds with its opposite member of its binding pair. (col. 1, lines 25-35 and 44-49).

Thus, the Gustafson assays work by contacting the diffraction grating with a sample analyte, illuminating the surface and measuring the light detected at the light diffraction angles. If the analyte binds to the active reagent, a diffraction grating is formed. Light detected at the diffraction angles correlates to the quantity of the analyte (col. 1, lines 63-67). Thus, it is the arrangement of the reagent molecules in parallel linear zones, and not labeled analytes, that allows the detection of the presence and quantity of an analyte. Nowhere does Gustafson teach or suggest that its diffraction grating may be used to detect more than one analyte, nor how one would use a diffraction pattern to do so.

To fully appreciate the differences between the products of the cited references, Applicants have annotated the following schematics: A) Applicants' rendering of a top view of the diffraction biograting taught in Gustafson based on Gustafson Fig. 1, and B) Fig. 1 from Chenchik which shows a top view of the biochip array:



Gustafson Chenchik

On the left, a top view of the biograting shown in Fig. 1 of Gustafson is shown. As can be seen from the schematic, a single binding agent ("target A" in the schematic) forms parallel linear zones of active and inactive target A. When contacted with a solution having the binding

partner of target A, the binding partners bind to form a diffraction grating. It is necessary that target A forms parallel linear zones so that when contacted with an analyte solution containing the opposite member of its binding pair, the bound pairs form a diffraction grating. The binding partner of target A is detected by the resulting diffraction pattern – if target A did not form parallel linear zones, the binding of target A and the partner would not form a diffraction grating. Thus, the entire context of Gustafson is premised on a single target bound on a substrate densely enough to form parallel lines that will diffract incident light when bound to its analyte partner.

Chenchik, by contrast, describes arrays of polymeric targets that can bind a plurality of proteins. The arrays are made up of patches of polymeric targets in discrete, known regions on a substrate (targets A, B, C, D, E, F, etc. in the schematic). Each position in the array represents a unique size (col. 5, lines 35-40). The assays work by contacting the arrays with a sample solution and detecting the presence or absence of a labeled probe bound to each target (col. 5, lines 35-40). The density of the array is low enough to provide adequate resolution of binding events with a probe carrying a variety of different labels (col. 5, lines 9-14). Chenchik discusses a wide variety of detection methods depending on the particular label used, e.g. fluorescent labels (col. 10, lines 38-44). Nowhere does Chenchik teach or suggest that a diffraction grating may be formed by any arrangement of its patches, nor that diffraction patterns may be used to detect the presence of proteins in the sample solution.

A Prima Facie case of Obviousness Has Not Been Made

A prima facie case of obviousness over the Gustafson in view of Chenchik has not been made for at least the following reasons, further discussed below:

1) Because the Examiner's proposed modification would render Gustafson unsuitable for its intended purpose, a proper suggestion or motivation to combine the references has not been asserted.

2) At least because Gustafson does not relate to labeled assays, one of skill in the art would not have been motivated to combine the references.

1) The Examiner's Proposed Modification Would Render Gustafson Unsuitable for Its Intended Purpose

The purpose of the substrates of Gustafson is to provide parallel zones of a binding reagent so that when contacted with a particular analyte, a diffraction grating is formed, the resulting diffraction pattern of which determines the presence and quantity of the analyte. Gustafson differs from the present invention at least by failing to include a plurality of different protein binding agents, and (for claims 73 and 99) fluoresencently labeled proteins. Chenchik is used to supply the array elements of different protein binding agents, as well as fluoresencently labeled proteins. The Examiner contends that one of skill in the art would be motivated to "include a

plurality of labeled proteins for the advantage of providing a high throughput format that provides two types of informations, which are the types of [protein] and the size of the expressed products."

As noted above, the two references describe very different arrangements of targets (alternating stripes of a single binding reagent or target versus discrete patches of different targets). There is no teaching or suggestion (nor indication provided by the Examiner) of how one might incorporate the multiple targets of Chenchik into the substrate of Gustafson; however Applicants submit that all of the possible manners in which one might carry out the Examiner's proposed modification would render Gustafson unsuitable for its intended purpose.

In order to form a diffraction grating when contacted with their binding partners, the binding agents would have to form parallel linear zones; any other arrangement would not result in a diffraction pattern under any circumstance and clearly render Gustafson unsuitable for its intended purpose. However, there is no suggestion in either reference and the Examiner has not specified, how the parallel lines would be formed. Would each binding agent be in a single line, or would all binding agents mixed together so that a single line would contain multiple binding agents?

Either way, there is no teaching or suggestion that the arrangement would form a diffraction grating upon contact with an analyte solution, and if so, the resulting pattern would provide useful information. Even if it were possible to form a diffraction grating using multiple different targets (and it is not clear that it is), there is no teaching or suggestion of how one would analyze the resulting presence or absence of a grating. For example, if substrate contained multiple targets, each forming single line, the absence of a diffraction pattern would provide little information – the analyte solution may still contain one or more of the analytes each of which bound to its respective partner to form for example, two lines at opposite ends of the substrate. One of skill would expect a diffraction grating to be formed only under a very narrow range of circumstances, i.e., only if most or all binding partners of the targets were present in the analyte solution and bound to their respective partners. The presence of a such diffraction pattern might provide information about the total amount of analytes present in the solution (and it is not clear that it would), but there is no indication or teaching that it would provide any information about the presence or quantity any one particular analyte.

In short, using multiple bind regents to construct the substrate of Gustafson would result in such little information being obtainable from the presence or absence of a diffraction pattern that the proposed modification would render Gustafson unsuitable for its intended purpose. Even if, for the sake of argument, it were possible to construct a diffraction grating using multiple binding agents some of which are bound to their respective analyte partners, it is far from clear from the combined teachings how one would analyze the resulting diffraction pattern to determine the presence and quantity of any or all of the analytes.

2) At least because Gustafson does not relate to labeled assays, one of skill in the art would not have been motivated to combine the references

The preceding argument underscores the fact that unlike the present claims and the Chenchik reference, Gustafson fundamentally does not relate to assays that employ multiple labeled probes. The arrangement of the binding agents of Gustafson and Chenchik, each crucial to the operations of its respective assays, are very different. To find that the particular biograting substrate of Gustafson is at all relevant to such labeled assays crosses the line into impermissible hindsight. The Examiner has contended throughout prosecution that Gustafson relates to labeled assays. Specifically, the Examiner contends the following section of Gustafson shows that the reference relates to signal amplification of a fluorescently labeled probe:

> "The term "diffraction grating", as used herein, is defined to include gratings which are formed in one or more immunological steps. For the method of this invention, the diffraction grating is formed directly by the conjugation of the non-light disturbing binding reagent on the insoluble surface with a light disturbing analyte." (col. 4, lines 41-46).

Applicants fail to see how this applies to fluorescently-labeled probes. While it may be possible to use a fluorescently-labeled analyte in the diffraction gratings of Gustafson, there would be no point in doing so. In the context of the Gustafson, a fluorescently labeled analyte is no more or less "light disturbing" than a label-free analyte; the assays work by measuring the diffraction of incident light on a diffraction grating created by the binding of the analyte. Whether sections of that diffraction grating are fluorescing is wholly inapposite to the operation of the assays of Gustafson.

This distinction is important because, as explained in prior Responses, the particular claimed configuration is designed to optimize the effectiveness of a fluorescence-based detection system. A person skilled in the art would not have seen any advantage in combining the teachings of Gustafson and any of the other references to which the Examiner has referred since Gustafson's teaching of the use of a flat substrate of silicon dioxide on reflective metal would have been viewed as specific to its particular diffraction-based assay. There is certainly no suggestion in the references of the benefit of a substrate surface configuration that increases reflectivity of the substrate surface to enhance fluorescent signal detection as described and claimed.

For at least these reasons, Applicants submit that a prima facie case of obviousness has not been made. In view of the foregoing, it is respectfully submitted that the rejections of all pending claims should be withdrawn.

Respectfully submitted,
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